CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40287

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION

ANDA APPROVAL SUMMARY

ANDA: 40-287

DRUG PRODUCT: Prednisolone Syrup USP

FIRM: Halsey Drug Company

DOSAGE FORM: Syrup STRENGTH: 15 mg/5mL

CGMP STATEMENT/EIR UPDATE STATUS:

The establishment evaluation request is acceptable for both Halsey and the manufacturer of the drug substance (Pharmacia & Upjohn) - M. Egas, 05-08-1998.

BIO STUDY:

Halsey had requested a waiver from the requirement for an in-vivo clinical bioequivalence study and waiver was granted by Division of Bioequivalence (S. Prahan, 07-09-1998).

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

The drug substance and the drug product are both USP compendial. FDA methods validation are not required.

STABILITY -
(ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?):

The containers used in the accelerated and room temperature studies are the same as proposed in the application.

LABELING:

Labeling issues have been resolved and all labeling is satisfactory (J. Barlow, 3-31-99).

STERILIZATION VALIDATION (IF APPLICABLE):

Halsey has submitted a microbiological protocol whereby Benzoic Acid content in the drug product is monitored on release and throughout stability as a measure of sterility. Halsey has submitted an study for Benzoic Acid below its label claim.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):

The executed batch, Lot 7G07E, was Liters gallons) in size. Approximately % of the executed batch was packaged in the proposed

container/closure systems.

The Drug Master File for the NDS is currently acceptable by review.

SIZE OF STABILITY BATCHES -
(IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch is identical to the bio batch.

PROPOSED PRODUCTION BATCH -
(MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):

The proposed production batch will be produced in a similar manner as the bio batch. The executed batch, Lot 7G07E, was .. Liters in size. Approximately 94% of the executed batch was packaged in the proposed container/closure systems. Master Batch Records for the scale-up batch size is Liters gallons) (page 251).

CHEMIST: A.J. Mueller, Ph.D. /S/ DATE: March 26, 1999

SUPERVISOR: V.A. Sayeed, Ph.D. DATE: 5/25/99

Date: March 26, 1999

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMISTRY REVIEW NO. 3 (three)

2. ANDA # 40-287

3. NAME AND ADDRESS OF APPLICANT

Halsey Drug Company, Inc.
Attention: George F. J. Scholes
1827 Pacific Street
Brooklyn, NY 11232

4. LEGAL BASIS FOR SUBMISSION

Prelone® Syrup (Prednisolone Syrup, 15mg/5mL); ANDA 89-081, Muro Pharmaceuticals

5. SUPPLEMENT(s)

Not applicable.

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Prednisolone Syrup USP, 15mg/5mL

8. SUPPLEMENT(s) PROVIDE(s) FOR:

Not applicable

9. AMENDMENTS AND OTHER DATES:

11-24-97 Original Submission
12-15-97 Applicant Correspondence
12-17-97 Applicant Correspondence
12-22-97 Agency Refuse to File Letter
12-30-97 Applicant Correspondence
03-20-98 Amendment to Original Submission
03-23-98 Accepted for Filing
04-09-98 Applicant Correspondence
04-13-98 Applicant Correspondence
04-20-97 Agency's Acceptance for Filing Letter
08-06-98 Agency's Deficiency Communication (Major)
09-25-98 Major Amendment from Halsey
03-04-99 Facsimile Amendment
05-12-99 Facsimile Amendment

10. PHARMACOLOGICAL CATEGORY
Glucocorticoid

11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s)

DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM

Syrup

14. POTENCY

15mg/5mL

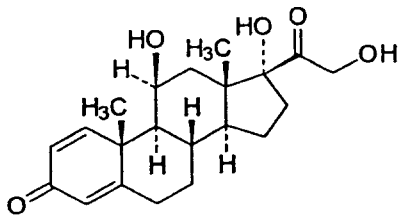
15. CHEMICAL NAME AND STRUCTURE

Prednisolone. Pregna-1,4-diene-3,20-dione, 11,17,21-trihydroxy-, (11β)-

Mol. Formula: $C_{21}H_{28}O_5$

Mol. Weight: 360.45

CAS Registry No. 50-24-8



16. RECORDS AND REPORTS

None

17. COMMENTS

None

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA is approved.

19. REVIEWER: DATE COMPLETED:

A.J. Mueller, Ph.D. May 18, 1999

APPEARS THIS WAY
ON ORIGINAL

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pages of trade

secret and/or

confidential

commercial

information

Chem Review #3

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-287 APPLICANT: Halsey Drug Company, Inc.

DRUG PRODUCT: Prednisolone Syrup USP, 15mg/5mL

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. There are many errors in the formula extensions (g/kg designations and wrong calculations for Propylene Glycol and Benzoic Acid for the Liter batch) shown on pages 95/96/111/536B/536C of your application and in Exhibits 3/4 of your March 20, 1998 correspondence to the Agency. Please review and correct these Tables and re-submit them.

2. Your have shown a % overage in the label amount of Prednisolone USP in your drug product manufacture documents. An overage of % Prednisolone is not recommended. Please reformulate your components and composition section to 100% of the labeled amount of Prednisolone and submit the appropriate documentation.

3. The information which you have supplied regarding resin is incomplete. In order to use this material, you should supply information regarding its suitability in containers which contains foods/drugs. This information can be supplied directly as an amendment to this application or by reference to Drug Master File.

4. You in-process protocol on page 348 of your application indicates samples are taken from the top/bottom of the bulk tank and only a single set of data are shown. Are the data an average of several values or are the sample mixed before testing? Please provide test data from each sample.

5. You have submitted two Certificates of Analysis (pages 422 and 424), wherein the CoA/page 424 indicates a status of "Finished Packaged Product" having a different Identification Test. Please provide data that the Identification Test shown on page 424 (Finished Packaged Product) is a valid Identification Test. Is the CoA format, shown on page 422, to be used with every lot of drug product manufactured by Halsey?

6. Please include a test for Delivered Volume as per the US Pharmacopeia 23 Test <698> for the packaged drug product.

7. Your Microbiology Protocol for Performing Anti-microbial Preservatives Effectiveness as shown on pages 552-555 to use Benzoic Acid as a preservative is incomplete. Please submit these data. You will also need to include Benzoic Acid content as part of your drug product release testing and Stability Protocol.

8. Please establish a test/specifications for individual and total degradants in your Stability Protocol. These requirements should be established based on data from your exhibit batch.

9. Please submit any room temperature stability test data which you may have available for the exhibit lot, Lot 7G07E.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Your analytical methodology is not identical to the US Pharmacopeial methods for the final drug product. Please be advised that the USP methods are the regulatory methods and will prevail in the event of any dispute.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research